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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

07 JAN 2005

Applicant's or agent's file reference 4-32572A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07350	International filing date *(day/month/year)* 08.07.2003	Priority date *(day/month/year)* 09.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D403/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2003	18.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Guspanova, J Telephone No. +49 89 2399-7834

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07350

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-78 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Relevant prior art**

D1: WO 00 031063 A (G. D. SEARLE & COMPANY, USA) 2 June 2000 (2000-06-02)
D2: WO 02 46184 A (LEDEBOER MARK ;VERTEX PHARMA (US); MOON YOUNG CHOON (US); SALITURO) 13 June 2002 (2002-06-13)

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03049542	19.06.2003	05.12.2002	10.12.2001

2. **Novelty**

The present application discloses pyrazolyl-pyrimidine derivatives of general formula (I) (claims 1-9), a process for the preparation thereof (claim 14), pharmaceutical compositions comprising such derivatives (claim 11) as well as their use in the treatment of a disease which responds to an inhibition of a protein tyrosine kinase, such as tumour (claims 10, 12 and 13).

Prior art D1 discloses a very large family of pyrazolyl derivatives of general formula (IA) (claims 93, 127 and 130) which partially overlaps with the general formula (I) presently claimed. The definitions of the substituents in the present application do correspond with the definitions given in D1 as follows:

Pyrimidinyl-NH-Ph-R_1	= R^3	= pyrimidinyl substituted by alkoxyarylamino
R_2	= R^1	= H, alkyl, heterocyclyl
R_3	= R^2	= R^{200}-aryl-R^{201}, wherein R^{200} is a bond and R^{201} is hydroxy, hydroxyalkyl, aminoalkyl
$R_{3'}$	= R^4	= H

The compound of example A-326 given on page 355 in document D1 falls within the scope

of the present claims 1-7. The process for the preparation of said compound falls within the scope of the present claim 14. However, it has been noticed, that there is a proviso given in the present claims 1-6 which excludes D1 compound of example A-326 from the scope sought for the protection. The proviso given in the present claim 7 is defined even broader and excludes all the compounds wherein R_1 is a radical R_4-lower alkyl-X-.

Document D2 discloses pyrazolyl-pyrimidine derivatives of general formula (I) given in claim 1, which formula differ from that of the present application in the position of a phenyl group attached to a pyrazole ring. The phenyl substituent is attached to a nitrogen atom of pyrazole in D2 compounds whereas it is attached to a carbon atom of pyrazole in the present compounds.

The whole subject-matter presently claimed is considered novel in view of D1 and D2, according to Article 33(2) PCT.

3. **Inventive step**

The problem underlying the present application resides in the provision of further pyrazolyl-pyrimidine derivatives useful for the treatment disease which responds to an inhibition of a protein tyrosine kinase, such as a tumour.

The closest prior art represented by D1 discloses a large family of compounds, which differ from those of the present application in the nature of the present substituent R_1. The compound of the Example A-325 wherein R_1 has the meaning of fluorine is considered to be the closest prior art derivative. D1 compounds are useful in treating p38 kinase mediated disorders. The data based on EGFRP assay procedure described on page 493 which are given for selected compounds can be found in Table 6.

Starting with compound A-325 of D1 the solution of the problem stated above resides in the introduction of different substituents into the phenyl ring. A list of possible substituents in phenyl ring is given in claim 1 of D2 on page 54. An introduction of some of these substituents into D1 compound A-325 would partially lead to the compounds presently claimed. Document D2 discloses compounds which are inhibitors of various protein kinases and thus useful in treatment of various disorders. D2 further teaches about an activation of serine/threonine kinases by dual phosphorylation of threonine and tyrosine

(page 2, lines 5-11) as well as about a role of JNK activation in various cancers, wherein VEGF is also mentioned (page 4, lines 1-18).

In other way round, prior art D2 can also be regarded the closest prior art. Starting with the closest compound of example 10, the solution of the problem stated above resides in moving the substituted phenyl ring from the nitrogen atom into the carbon atom of pyrazole ring. The presence of such a phenyl ring at carbon atom on pyrazole ring is known from D1.

Since D1 and D2 compounds are useful as inhibitors of various protein kinases, the person skilled in the art would take the teaching of both documents into consideration in order to provide further compounds useful in treatment of a disease which responds to an inhibition of a protein tyrosine kinase. The skilled person would foreseen the activity of the compounds presently claimed with a reasonable expectation of success.

The solution of the problem stated above seems to be a combination of the features already known in the art and is therefore considered obvious in view of D1 and D2.

An inventive step according to Article 33(3) PCT cannot be acknowledged for the whole scope claimed in the present application.

4. **Clarity**

The following inconsistency between the description and the claims according to Article 6 PCT has been found in the present application.
The compounds of Examples 91,109 and 116 do not fall within the definition of substituent R^1 given in claim 1.

The said inconsistencies may throw doubt on the extent of the protection south for the present application. Therefore, they should be removed either by broadening the claims or removing the "excess" subject-matter from the description.